International Journal of Infectious Diseases 92 (2020) 271–272

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Letter to the Editor

Reply to: Single-dose rifampicin and BCG to prevent leprosy

Dear Editor,

We thank Lockwood et al. for their comments on our article 'Effectiveness of single-dose rifampicin after BCG vaccination to prevent leprosy in close contacts of patients with newly diagnosed leprosy: A cluster randomized controlled trial' (Richardus et al., 2019), and greatly appreciate the opportunity to reply.

First, the authors compare the MALTALEP trial and the COLEP trial (Moet et al., 2008), because both trials address chemoprophylaxis in leprosy with single-dose rifampicin (SDR). Yet there are crucial differences that render direct comparison precarious. The COLEP trial examined the effectiveness of SDR (alone) given to contacts of leprosy patients in and outside the household. Overall, a significant reduction in the incidence of leprosy of 57% (95% CI: 33–72%; P = 0.0002) was seen. This result was observed after two years and decreased the incidence of leprosy among the contacts to the incidence of leprosy in the general, untreated population, and this was sustained at 4- and 6-years follow-up. The authors' remark that *"The COLEP trial identified that the short-term benefits of SDR were only significant in more distant contacts of index cases"* is simply not factual. In contrast, the benefit of SDR was long-lasting and the statistically significant primary outcome measure of 57% applied to all contacts collectively. For a detailed explanation of the COLEP trial we refer to our previous communication (Richardus and Smith, 2018).

A decade later, the MALTALEP trial had a very specific context, different from the COLEP trial: it was based on the observation that BCG vaccination provided to contacts of leprosy patients in the long term had shown a protective effect against leprosy. However, the possibility of leprosy appearing during the first year after vaccination, before BCG's protection was effective, needed further study. The aim of the MALTALEP trial was to determine whether possible excess cases in the first year after immunoprophylaxis (with BCG) could be prevented with chemoprophylaxis (with SDR) without affecting BCG's protective effect. Thus, the results of the MALTALEP trial should be considered in this light, where contacts were first given BCG, and subsequently SDR, in one arm of the trial. Thus, contacts receiving SDR in this study were immunologically different from those receiving this form of chemoprophylaxis in the COLEP study. Furthermore, the results are confounded because one third of all new leprosy cases among contacts arising after BCG appeared (unexpectedly) already 8–12 weeks after BCG vaccination, and (crucially!) ***before*** the administration of SDR. The primary outcome measure of new leprosy cases at 1 and 2 years was not significantly different (at a level of 5%) between the two arms of the trial.

In the MALTALEP article we described the reduction in PB leprosy (most of our new patients) of 42% in the SDR arm as notable, although not statistically significant due to insufficient statistical power. Regarding MB leprosy, we indeed found more cases at 1- and 2-years follow-up in the SDR arm of the trial (5 *vs.* 3 and 6 *vs.* 0, respectively). This is certainly peculiar. Importantly, the numbers are very low, and we hesitate to draw any conclusions on findings of secondary subgroup analysis, particularly about clinical relevance (Burke et al., 2015). Furthermore, MB was diagnosed initially by lesion count according to the WHO classification system and subsequently tested for bacterial index (BI) by slit skin smear. Of all MB cases in the MALTALEP trial (before and after SDR intervention), only one case had a BI of 2+ (classified as borderline lepromatous leprosy). All others were negative (BI zero) and classified as borderline tuberculous leprosy (BT).

The authors end with a sweeping conclusion that *"the evidence for SDR as a strategy to prevent leprosy or achieve the target of zero transmission of M. leprae remains limited"*. We hope to have made clear that this opinion cannot be based on the findings of the MALTALEP trial, because this trial was primarily about the possibility of SDR augmenting the immunoprophylactic effect of BCG vaccination. For more information on chemoprophylaxis with SDR we refer to the 2018 WHO Guidelines for the Diagnosis, Treatment and Prevention of Leprosy, in which a recommendation for chemoprophylaxis with SDR is given based on the GRADE process (Anonymous, 2018).

Conflict of interest

None.

Funding source

None.

Ethical approval

Not applicable.

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Received 27 January 2020